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Pharmacotherapy of severe asthma

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Abstract

Severe asthma is a complex and heterogeneous phenotype where management can be challenging. While many patients with severe asthma respond to high-dose inhaled corticosteroids in combination with a long-acting β -agonist, there remains a significant subset of patients that require oral corticosteroids to control symptoms. Alternative therapies are needed to help reduce the need for continuous oral corticosteroids; however, there are currently very few effective options. Several new alternatives to oral corticosteroids have been evaluated in severe asthma as add-on to conventional therapy. These include macrolide antibiotics, omalizumab, tumor necrosis factor- α inhibitors, cytokine receptor antagonists, and bronchial thermoplasty. The challenge with these entities is determining the appropriate phenotype of severe asthma where effectiveness is demonstrated, given the significant heterogeneity of the disease. Therefore, there is a crucial need to better understand the mechanisms and pathophysiology of severe asthma so more effective immunomodulators and biologic therapies can emerge.

Introduction

Although severe asthma is estimated to be present in less than 10% of all asthmatics, these patients have the greatest morbidity and consume an overwhelming portion of health care costs [1]. There has been much debate and effort in defining severe asthma both in the United States and Europe [2,3]. What has emerged is that patients with severe asthma represent a heterogeneous group with multiple phenotypes. Although the American Thoracic Society and European Respiratory Society differ in their exact definitions of severe asthma, both define a patient with persistent symptoms despite the use of adequate controller therapy, including multiple courses or continuous use of oral corticosteroids. In order to assist in characterizing and treating these patients, the American Thoracic Society has developed a working definition for refractory asthma [Table 1]. Despite considerable progress in the understanding of these complex phenotypes, managing patients with severe asthma remains extremely challenging. The purpose of this article is to review some of the more recent advances in the pharmacotherapy of severe asthma.

Current treatment options

When evaluating patients with severe asthma, it is important to ensure that the lack of response to corticosteroids is not due to other factors. This should include evaluating for alternative diagnoses, ensuring medication adherence, and evaluating for the presence of cigarette smoking, allergy exposures, and co-morbid conditions. This latter category includes gastroesophageal reflux disease (GERD), rhinitis/sinusitis, obstructive sleep apnea, and/or obesity. Regarding GERD, a recent placebo-controlled trial demonstrated that empiric treatment of GERD with a proton-pump inhibitor did not improve asthma control in patients with severe asthma and no clinical symptoms of reflux [4••]. Other studies have also failed to find marked improvements in asthma control when attempting to control reflux in symptomatic patients with moderate–severe asthma [5,6]. With regard to obesity, recent studies suggest that obesity results in a corticosteroid-resistant state where other medications may be more efficacious, such as leukotriene modifiers [7,8•].

The mainstay of asthma therapy remains inhaled corticosteroids and β_2 -agonists [9]. The current asthma management guidelines suggest a step-up approach beginning with inhaled corticosteroids for persistent asthma [9]. For patients with severe asthma, the standard treatment is high-dose inhaled corticosteroids combined with a long-acting β -agonist (LABA), often given as single inhaled device. The addition of a LABA has been shown to reduce the required dose of inhaled corticosteroids by 57% [10]. Some studies have suggested that patients with asthma who are homozygous for arginine at position 16 of the β_2 -adrenergic receptor benefit less from the use of LABAs as compared to those homozygous for glycine [11]. However, two recent large studies failed to show evidence of a pharmacogenetic effect of β -receptor polymorphism at position 16 on the clinical response to salmeterol [12•,13•]. Other recommended add-on therapies include leukotriene receptor antagonists, zileuton or theophylline [9]. If a patient's symptoms continue to persist or worsen, current recommendations are to consider oral corticosteroids, despite their significant side effect profile [14]. If a patient requires continuous oral corticosteroids, existing guidelines offer little insight for alternative therapies.

Emerging treatment options: macrolide antibiotics

Studies have established that *C. pneumoniae* and *M. pneumoniae* infections have important clinical relevance in acute exacerbations as well as in disease severity and chronicity [15–17]. While macrolide antibiotics would be the treatment of choice for these infections, they also, interestingly, have been shown to reduce neutrophilic inflammation [18–21]. This dual effect has led to its investigation in treating patients with severe asthma. While some studies clearly suggested the benefit of macrolide therapy in chronic asthma, a Cochrane review in 2005 concluded that there was insufficient evidence to advocate the use of macrolides as an add-on therapeutic option [22–25]. In a more recent, placebo-controlled study of 45 subjects, clarithromycin was found to significantly reduce airway concentrations of IL-8 and neutrophil numbers and improve quality-of-life scores in patients with severe non-eosinophilic asthma compared to placebo [26•]. Whether macrolides may have a benefit in this particular phenotype of asthma with a more neutrophilic pathology is still under investigation.

Emerging treatment options: omalizumab

In recent years, newer biologics have been tested in patients with severe refractory asthma. Omalizumab is the first licensed humanized monoclonal antibody directed against IgE, and is approved by the Food and Drug Administration (FDA) for patients over 12 years of age with moderate-to-severe persistent allergic asthma. The addition of omalizumab to other controller medications has been shown to improve control of allergic asthma whose symptoms were not being controlled with high-dose combination therapy [27–30]. These results were confirmed through a 2006 Cochrane meta-analysis, showing that omalizumab added to usual therapy is effective in the treatment of moderate–severe allergic asthma and results in a significant reduction in inhaled corticosteroid and rescue medication [31]. However, in patients with severe asthma requiring oral corticosteroids, the meta-analysis failed to show any difference in asthma exacerbations or reduction in the oral corticosteroid dose [31]. The major side effect of omalizumab remains the possibility of anaphylaxis and therefore patients should be observed for a period of time following injection [32••]. There has also been concern about malignancy; however, in a recent safety review clinical trial data did not support an increased risk of malignancy in those treated with omalizumab [33].

Emerging treatment options: anti-cytokine therapies

Tumor necrosis factor- α (TNF- α) has been shown to be involved in airway inflammation and has been found to be elevated in subjects with severe asthma [34]. Corticosteroids characteristically fail to reduce TNF- α in asthmatic airways in severe asthma [35]. Therefore, there has been considerable interest in evaluating medications directed against TNF- α . In two small studies, etanercept, a soluble TNF- α receptor fusion protein, was found to improve asthma symptoms, lung function and bronchial hyperresponsiveness in patients with severe asthma [36,37•]. In a more recent and larger placebo-controlled study, etanercept failed to show any significant improvements in lung function, bronchial airway hyperresponsiveness, and asthma quality-of-life [38••]. In another large placebo-controlled study using golimumab, a human monoclonal antibody against TNF- α , failed to show improvement in lung function or exacerbation rates in patients with severe asthma. The unfavorable risk–benefit profile led to early discontinuation of the study [39••]. In a *post-hoc* analysis, subjects who demonstrated a bronchodilator response to β_2 -agonists of greater than 12% demonstrated fewer exacerbations. In addition, TNF- α also appears to be a prominent mediator in obese asthma [40]. Thus, the obese patient with asthma could represent a phenotype of asthma that may benefit from TNF- α inhibition, but this will require further investigation.

Daclizumab, a humanized monoclonal antibody directed against the interleukin-2R α chain, has recently been evaluated in moderate-to-severe persistent asthma [41••]. In a placebo-controlled proof of concept study of 115 patients with moderate-to-severe persistent asthma, treatment with daclizumab resulted in improved lung function and reduced exacerbations in the setting of inhaled corticosteroid withdrawal. The mechanism of its action is probably through inhibiting the generation of pro-inflammatory cytokines from T cells [41••]. Further studies are needed to determine its potential efficacy as add-on therapy in asthma.

Mepolizumab is a humanized monoclonal antibody directed against interleukin-5, which is a potent eosinophilic cytokine and growth factor. In three previous clinical trials, mepolizumab failed to show effect in patients with moderate–severe asthma [42–44]. More recently, two studies more closely evaluated the use of mepolizumab in patients who had refractory asthma and evidence of eosinophilic airway inflammation as demonstrated by 3% of eosinophils in induced sputum [45••,46]. In the larger study of 61 patients, mepolizumab decreased exacerbation rates and improved asthma quality-of-life scores but failed to improve lung function [45••]. In the smaller study of 21 patients, subjects using mepolizumab were able to significantly reduce oral prednisone dose compared to placebo [46].

Pitrakinra is an interleukin-4 variant that targets Th2 inflammation through inhibiting the binding of interleukin-4 and interleukin-13 to the interleukin-4R α receptor complex. Two independent studies evaluated whether subcutaneous injection or inhalation could improve symptoms in patients with moderate asthma [47••]. Only, the patients who received pitrakinra via nebulization had significantly attenuated decrease in FEV₁ after allergen challenge compared to placebo. Patients who received pitrakinra subcutaneously had fewer asthma-related adverse events requiring β -agonist rescue. In both studies, pitrakinra seemed to be well tolerated. While the results of these studies are encouraging, it remains to be investigated whether pitrakinra could have a role in severe asthma.

Emerging treatment options: bronchial thermoplasty

Another recent therapeutic approach involves using bronchial thermoplasty in patients with severe asthma. This involves the patients to undergo bronchoscopy coupled with the application of radio frequency heat to the airway to reduce their airway smooth-muscle mass. In a study published in 2007, bronchial thermoplasty improved asthma control in a group of moderate-to-severe asthmatic subjects [48]. In a recently published second study in a separate group of similar subjects that included a sham bronchoscopy, bronchial thermoplasty was associated with an improvement in asthma quality-of-life and a reduction in severe exacerbation compared to patients undergoing a sham procedure [Figure 1a and b] [49••]. In another study out of the United Kingdom, bronchial thermoplasty was associated with significant improvements versus control subjects in rescue medication use, prebronchodilator FEV₁% and Asthma Control Questionnaire scores [50]. This procedure has recently been approved by the FDA as an alternative treatment in patients with severe refractory asthma.

Conclusions

While most patients with mild to moderate asthma can be managed successfully with combination therapy, there still remains a subset of patients with severe asthma that require oral corticosteroids to improve asthma control and decrease exacerbations. Given the significant side effects associated with long-term oral corticosteroid use, alternatives are crucial in this population. Omalizumab offers a possible alternative for patients with allergic asthma, but more investigation to determine the best candidates *a priori* are necessary. Mepolizumab has shown promise for patients with evidence of eosinophilic airway

inflammation by assessment of induced sputum. Other cytokine therapies such as pitrakinra or daclizumab need further investigation while TNF- α inhibitors may be beneficial in obese asthmatics. For patients with neutrophilic inflammation, macrolide antibiotics seem to be most effective. Finally, bronchial thermoplasty is now available in some centers and could offer some benefit for those resistant to other therapies. Effort aimed at more thorough phenotyping of these severe asthmatic subjects, both clinically and pathologically, will allow for more directed, effective therapy in this very challenging population.

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Figure 1.

(a) Change in Asthma Quality-of-Life Questionnaire (AQLQ) score over 12 months following treatment with bronchial thermoplasty (BT) compared to sham. *Posterior probability of superiority = 97.9%. (b) Rate of health care utilization events during the post-treatment period. Open bars, sham; shaded bars, bronchial thermoplasty. All values are means $\pm$ SEM. *Posterior probability of superiority 5 95.5%. †Posterior probability of superiority 5 99.9%. Figure adapted from reference [49••].

Table 1 American Thoracic Society consensus definition of refractory asthma^a

Major characteristics

- Treatment with continuous or near-continuous (≥ 50% of the year) oral corticosteroids
- Requires high-dose inhaled corticosteroids

Minor characteristics

- Requires daily treatment with controller medication in addition to inhaled corticosteroids
- Requires short-acting β -agonists on a daily or near-daily basis
- Evidence of persistent airway obstruction ($FEV_1 < 80\%$ predicted, diurnal PEF variability $> 20\%$)
- One or more urgent care visits for asthma per year
- Three or more oral corticosteroid 'bursts' per year
- Prompt deterioration with ≥ 25% reduction in oral or inhaled corticosteroid dose
- Near-fatal asthma event in the past

^aDefinition requires that at least one major characteristic and two minor characteristics be met. In addition, other potential diagnoses have to be excluded, other exacerbating factors be treated and patient compliance ensured.